

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Briefing Document for FDA Advisory Committee Meeting

**Benefit-risk considerations in the management of pain using prescription
acetaminophen-containing combination analgesic products marketed by
Johnson & Johnson**

**ULTRACET[®] (tramadol hydrochloride/acetaminophen) Tablets
(RWJ-26898/RWJ-03465)**

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1. INTRODUCTION

On April 23, 2009, the Food and Drug Administration (FDA) announced that it would be holding a Public Advisory Committee Meeting, on June 29-30, 2009, to discuss liver injury related to the use of acetaminophen in both over-the-counter (OTC) and prescription products. FDA has stated that acetaminophen is an important drug used to treat pain and fever in both the OTC and prescription setting and that they are not seeking to remove it from the market. FDA has also stated that the risk of developing liver injury to the individual patient who uses the drug according to directions is very low. However, acetaminophen-containing products are used extensively, thereby, making the absolute number of liver injury cases a public health concern. According to the announcement, FDA's discussion with the Advisory Committee Members will focus on why acetaminophen overdoses occur and FDA's proposed options to address this public health concern.

On May 22, 2009, the FDA issued a Background Package for June 29-30, 2009 Meeting, which included the following:

- A scientific review paper and recommendation statement, which was finalized February 26, 2008, from the Acetaminophen Hepatotoxicity Working Group, of Center for Drug Evaluation and Research (CDER).
- An Options Paper written by CDER staff to summarize the full scope of interventions that FDA has considered

In the latter, "Options Paper", the CDER staff enumerated and described options of actions for discussion at the upcoming Advisory Committee Meeting. The Options pertinent to prescription acetaminophen containing analgesic products are:

- Reducing the amount of acetaminophen recommended as a daily dose for OTC, and perhaps also prescription products. Alternatively, any amount of acetaminophen greater than 325 mg per tablet (650 mg recommended dose) could be restricted to prescription only.
- Require unit-of-use packaging for prescription products. Unit-of-use packaging would enable FDA to standardize the information laid out on the prescription label, warnings, and description of active ingredients (e.g., use of the word acetaminophen instead of the abbreviation "APAP").
- Expand product warning information on prescription products, requiring package labeling to identify acetaminophen as an ingredient, consistently and prominently (and not use different terms, such as APAP)
- Eliminate combination OTC and/or prescription products that contain acetaminophen.

The purpose of this document is to highlight some important considerations regarding prescription combination analgesics manufactured and distributed by

Johnson & Johnson, such as ULTRACET® (tramadol HCl/acetaminophen), TYLENOL® with Codeine (acetaminophen/codeine) and TYLOX® (oxycodone/acetaminophen), and to assist the Advisory Committees and the FDA in reaching an appropriate plan of action. Such a plan would balance the mitigation of the risks with the preservation of benefits in the management of pain with prescription acetaminophen-containing analgesic products.

2. THE ROLE OF PRESCRIPTION ACETAMINOPHEN-CONTAINING ANALGESIC PRODUCTS IN THE MANAGEMENT OF PAIN

Pain, both acute and chronic, affects millions of Americans. Chronic pain alone is estimated to affect 100 million people in the United States.¹ While there are many analgesics available to treat pain, no single analgesic has been shown to relieve all types of pain in all patients. Another limitation of available analgesics is that they all have limiting adverse events. Due to physician and patient fear of these adverse events, many patients in the United States are undertreated for their pain.^{2,3,4,5}

An approach to improving pain control that addresses concerns with adverse events is the use of a combination of analgesics. In addition to the potential safety benefits of combination therapy, other potential advantages to use of a combination of analgesic drugs include the potential to overcome tolerance, improve efficacy, and decrease time-to-onset limitations of monotherapy.⁶ Many types of pain are multimodal in their physiology with various pain pathways and chemical mediators contributing to a given type of pain. By combining analgesics with different mechanisms of action, the potential to target the various mechanisms contributing to a given type of pain are increased. As a result, combinations of analgesics with different mechanisms of action may result in additive or even synergistic pain relief. Furthermore, if a fast-onset but short-acting and a slower onset but longer-acting analgesic are combined, the outcome may be a shorter time to onset of pain relief and a longer duration of pain relief. The multimodal pain relief provided by combination therapy may permit use of reduced doses of each analgesic resulting in a decreased risk of adverse events while providing comparable or better analgesia than the individual components. In addition, the use of a combination analgesic provides a mechanism to transition patients from one single-entity analgesic to another. The World Health Organization,⁷ as well as numerous professional associations including the National Comprehensive Cancer Network,⁸ American Pain Society,⁹ Institute for Clinical Improvement,¹⁰ and American College of Rheumatology,¹¹ recommend use of a combination of analgesics in their pain management guidelines.

Combination analgesia can be provided by administering the individual components separately or by using a fixed-dose combination product. There are several benefits to using a fixed-dose combination product rather than administering the individual

components separately. Compared with administration of the individual components, fixed-dose combination analgesic products may promote better compliance since the number of medications that a patient must take is reduced. In addition, medication errors may be reduced. With some analgesic combinations, the best efficacy and safety profile may be achieved with specific ratios of one analgesic to another; by providing both analgesics in one formulation, use of the most appropriate ratio is ensured.⁶

Acetaminophen is often used as the non-opioid analgesic-antipyretic in analgesic combination products. It has an excellent safety profile when the labeled dosage is used and is not subject to the tolerance, addiction, or toxicity of opioid analgesics. Moreover, single or repeated therapeutic doses of acetaminophen have no effect on the cardiovascular or respiratory systems. Acetaminophen, in contrast to nonsteroidal anti-inflammatory drugs, has not been associated with acid-base changes, gastric irritation, erosion or bleeding, and has no effect on platelets, bleeding time, the excretion of uric acid, or interference with the effect of some antihypertensive medications. The clinical rationale driving the combination of acetaminophen and other prescription analgesics is the assumption that the combination of a rapid onset, short-acting agent (i.e., acetaminophen) with a slower onset, longer-acting agent (i.e., tramadol) will provide substantial therapeutic benefit over either component alone.

Section 3 provides an example of this in the case of the tramadol/acetaminophen combination product.

In addition, acetaminophen-containing combination products have been the focus of several meta-analyses. Section 6 provides details on two of these meta-analyses, which investigated combination products with different doses of acetaminophen.

3. EFFICACY AND SAFETY OF TRAMADOL AND ACETAMINOPHEN COMBINATION PRODUCT: RESULTS OF FACTORIAL-DESIGN TRIALS

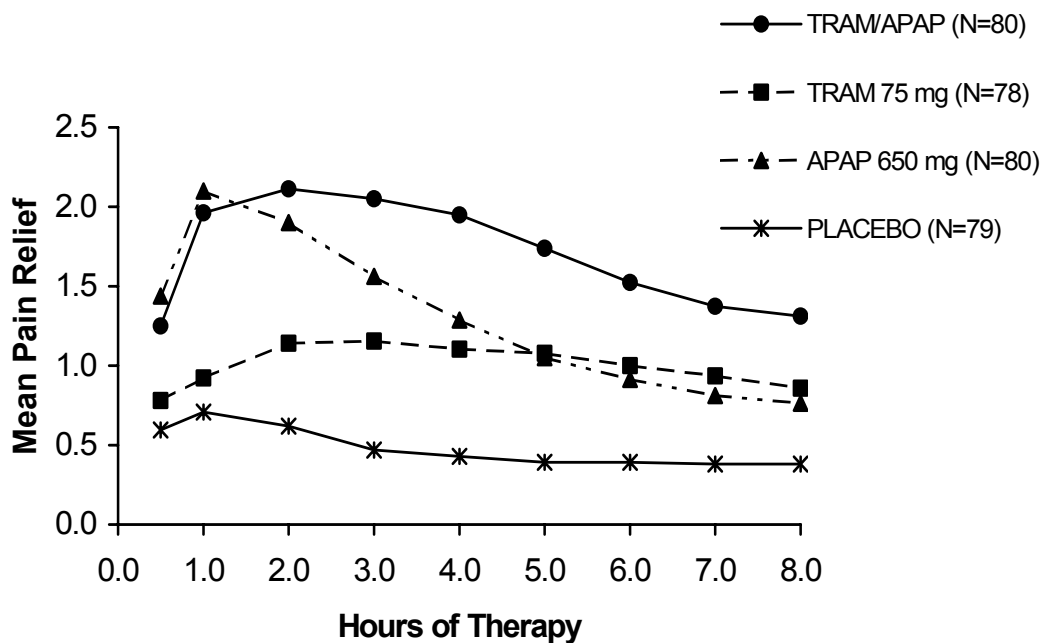
Tramadol hydrochloride (tramadol) is a centrally-acting analgesic that is widely marketed throughout the world. Tramadol has been shown to be effective in treating a wide variety of pain conditions, including the management of both nociceptive and neuropathic pain, when treatment with strong opioids is not required. The pharmacokinetic and pharmacodynamic profile of tramadol shows peak activity in two to three hours with an elimination half-life and duration of analgesia of about six hours. Acetaminophen yields peak plasma concentrations between 0.4 and one hour and has an elimination half-life of two to three hours. Combination of tramadol with a rapid-onset and short-acting analgesic such as acetaminophen provides substantial patient benefit over either component alone. In the US, the tramadol/acetaminophen combination is indicated for

the short-term (five days or less) management of acute pain. In the management of acute pain, rapid onset combined with prolonged analgesia is desirable.

ULTRACET® contains 37.5 mg of tramadol hydrochloride and 325 mg of acetaminophen in a single tablet and is marketed by Ortho-McNeil Pharmaceutical, Inc. On August 15, 2001, ULTRACET® was approved for marketing in the United States for the short-term (five days or less) management of acute pain, with a dosing regimen of two tablets every four to six hours as needed for pain relief, up to a maximum of eight tablets per day (maximum total daily dosage of tramadol is 300 mg and of acetaminophen is 2600 mg). Since 2004, generic formulations of tramadol plus acetaminophen have been approved for use in the US.

Three single-dose dental pain studies^{12,13,14} in subjects with multiple molar impactions compared the analgesic efficacy of the tramadol/acetaminophen combination product (75 mg of tramadol/650 mg of acetaminophen) to each of the components (i.e., to tramadol 75 mg and acetaminophen 650 mg) and to placebo in the treatment of moderate to severe pain. In each of these full factorial-design trials, tramadol/acetaminophen was statistically significantly superior to placebo and to each component alone for the three summary efficacy variables: areas under the curve of pain relief against time, pain intensity difference against time, and pain relief plus pain intensity difference against time at the 0 to 8 hour interval. Figure 1 displays the mean pain relief scores from one of the single-dose oral surgery pain studies and demonstrates the added effectiveness of the tramadol/acetaminophen combination.¹² The time course of activity for tramadol/acetaminophen can be described by a rapid onset and steady rise in pain relief to peak effect, generally within two to three hours, followed by prolonged analgesic activity (pain relief persists throughout dosing interval). This pattern is a composite of the time-effect curves associated with each of the components in the combination. Two randomized, double-blind studies, one in low back pain and the other in dental pain.^{15,16} also support the efficacy of a combination of acetaminophen and tramadol versus the marketed strengths of tramadol 50 mg.

Figure 1: Mean Hourly Pain Relief Scores^a Demonstrating Added Efficacy of the Tramadol 75 mg/Acetaminophen 650 mg Combination¹²



APAP=acetaminophen, TRAM=tramadol

^a Pain relief rating scale: 0=none; 1=a little; 2=some; 3=a lot; 4=complete. Displayed scores based on last observation carried forward analysis.

The three dental pain studies, as well as the two published studies, all used a dose ratio of tramadol to acetaminophen of 37.5 mg to 325 mg in the combination product. The use of this dose ratio was based on prior experience with tramadol and acetaminophen individually, as well as on the results of three pilot studies conducted early in the course of the development of the tramadol/acetaminophen combination product.¹⁷

As reported in the Integrated Summary of Safety (ISS)¹⁸ in the original NDA submission, the tramadol/acetaminophen combination was well tolerated in subjects with acute pain and had an adverse event profile that was consistent with the known side effects of the individual components.

Two additional published studies have demonstrated a lower incidence of adverse events with the combination product than that with tramadol alone, using the marketed formulation of 50 mg per tablet. In a multicenter, randomized, double-blind, parallel-group study which compared the use of the combination of tramadol 37.5 mg and acetaminophen 325 mg with tramadol 50 mg alone in patients with lower back pain, there was equal efficacy but a significantly lower overall incidence of adverse events in the combination group than in the tramadol monotherapy group (50.8% vs 73.3%, $p=.019$).¹⁵

There was also a significantly lower incidence of nausea (13.6% vs 35.0%, $p=.012$) and dizziness/vertigo in the combination group (5.1% vs 25.0%, $p=.006$). In the other randomized, double-blind study in patients with dental pain, the combination product was superior in efficacy to tramadol alone and placebo. The overall incidence of adverse events was 54% with tramadol/acetaminophen and 64% with tramadol alone; there was also a significantly lower incidence of nausea in the combination group than in the tramadol -alone group (33% vs. 46%, $p=.019$).¹⁶

4. HEPATOBIILIARY SAFETY OF ULTRACET® (TRAMADOL HCL + ACETAMINOPHEN) TABLETS IN CLINICAL TRIALS

An analysis of treatment-emergent adverse events (TEAEs) was conducted with data from 19 studies (10 acute pain studies: and 9 chronic pain studies) in 3,003 tramadol/acetaminophen-exposed subjects with acute or chronic pain.

Among the 3,003 tramadol/acetaminophen-exposed subjects, the following TEAEs (WHO-ART Preferred Terms [PTs]) related to the hepatobiliary system were reported with an incidence of less than 1%: Hepatic Function Abnormal, SGPT (ALAT) Increased, SGOT (ASAT) Increased, and (Hyper)Bilirubinaemia.¹⁹

Of the 3,003 tramadol/acetaminophen-exposed subjects in all the acute and chronic pain studies combined, 20 (1%) reported TEAEs related to the hepatobiliary system. The most frequent TEAE in this group was "hepatic function abnormal" (Table 1). The events were reported to have occurred as early as Day 12 and as late as Day 249. Bilirubinemia was reported in 2 subjects, with 1 subject in whom hyperbilirubinemia, with no elevations in transaminases or alkaline phosphatase, was reported separately on Days 31, 88, and 249. None of the TEAEs was a serious adverse event. None of these cases involved abnormal post-baseline increases in serum concentrations of either hepatic transaminases or bilirubin greater than 3 times the upper limit of normal (ULN). The respective reporting investigators assessed most of these TEAEs as possibly-related to study medication. All of the events resolved, except for the 1 subject who had multiple events of bilirubinemia, which was persisting as of the Final Visit on Day 718.

Table 1: Incidence of TEAEs Related to the Hepatobiliary System: All Tramadol/Acetaminophen-Exposed Subjects in Acute and Chronic Pain Trials

Preferred Term*	TRAM/APAP (N=3,003)	
	N	(%)
Hepatobiliary System-related	20	(1)
Hepatic Function Abnormal	7	(<1)
SGPT (ALT) Increased	5	(<1)
SGOT (AST) Increased	3	(<1)
Phosphatase Alkaline Increased	3	(<1)
Bilirubinemia	2	(<1)

* WHO-ART Preferred Term

Clinical laboratory tests were not performed in the single-dose pain trials. For the 9 multiple-dose acute and chronic pain studies, involving 2259 subjects, changes in markedly abnormal hepatobiliary laboratory test values (LFTs) fell into three categories: values that increased from the pretreatment value (121 subjects), values that decreased from the pretreatment value (67 subjects), and abnormal-high pretreatment values that remained abnormally high during the respective studies (81 subjects). Across these studies, for subjects whose LFTs increased from the pretreatment value, the majority had elevations in a single analyte.²⁰

The incidence of markedly abnormal serum transaminase values, that is, >75 mg/dL (2x Upper Limit of Normal [ULN]) and Increase of $\geq 100\%$, was <1%. There were no subjects in whom increases in serum total bilirubin exceeded > 2x ULN or increases were in excess of 100% of the baseline value (Table 2). Five subjects who had markedly abnormal elevations in LFTs were reported as TEAEs related to the hepatobiliary system (see Appendix 1).

Table 2: Incidence of Markedly Abnormal Hepatobiliary Laboratory Test Analyte Values: All Tramadol/Acetaminophen-Exposed Subjects in Nine Multiple-dose Acute and Chronic Pain Trials

Analyte	Criteria ^a			TRAM/APAP N/N (%) ^b
Liver Function				
ASAT	>75 mg/dL	and	Increase of $\geq 100\%$	6/2259 (<1%)
ALAT	>75 mg/dL	and	Increase of $\geq 100\%$	16/2259 (1%)

^a A value was considered markedly abnormal if it met both the absolute value criteria and the specified change from baseline criteria.

^b Values represent (no. Of subjects with markedly abnormal analyte value)/(all subjects who had the analyte measured). Percent of subjects with data available who had marked abnormality is given in parentheses.

TRAM = tramadol; APAP = acetaminophen.

5. COMPARISON OF ABUSE RELATED CHARACTERISTICS OF TRAMADOL WITH OTHER OPIOIDS

The abuse risk of tramadol has been extensively investigated utilizing data from epidemiological and post-marketing surveillance studies, including the WHO

Collaborating Centre for International Drug Monitoring, the Grünenthal Worldwide Spontaneous Reporting Database, a post-marketing surveillance program on tramadol abuse (The Researched Abuse Diversion and Addiction Related Surveillance (RADARS[™]) system and an Independent Steering Committee (ISC)^{21,22} in the USA, the Drug Abuse Warning Network (DAWN) in the USA, the Substance Abuse Warning System (SAWS) in Germany, the Toxic Exposure Surveillance System (TESS), and the National Forensic Laboratory Information System (NFLIS).

These studies are consistent in showing minimal levels of abuse of tramadol and of tramadol/acetaminophen.

A 1992 expert report on the abuse liability of tramadol from the Centre of the Chemical Dependence of Medicine in Baltimore, Maryland, concluded that the abuse potential of tramadol is low for four basic reasons: i) the low potency to produce opioid-like subjective effects and euphoria with respect to its analgesic potency; ii) the non-opioid component of tramadol is not related with psychotropic or reinforcing effects; iii) 300 mg intramuscular doses in post-addicts were not euphorogenic; and iv) the delayed onset of action in comparison with prototypic opioids. At a dose of 300 mg, tramadol was not rated as likeable and did not produce other opioid effects.

Tramadol's abuse risk has not increased since 1992. The relative frequency of tramadol abuse (ie, number of abuse reports versus sales) is in the same range in 2008 as it was in 1992, when the WHO assessed that no significant abuse had been reported. This has been consistently confirmed by the available, evidence-based epidemiological data.

Recent data specific to the RADARS System, as an example, is presented in the graphs below (Figure 2, Figure 3, Figure 4, Figure 5). This active surveillance program collects, compiles, analyzes and maintains certain de-identified health care and other information in proprietary databases containing data from 4 signal detection system networks including a poison center network, a drug diversion network, a key informant network, and an opioid treatment program network. An objective of the RADARS System is to identify abuse, misuse and diversion rates for oxycodone, hydrocodone, morphine, hydromorphone, fentanyl, buprenorphine, methadone and tramadol.

Through the period including 3Q08, tramadol rates of abuse, misuse, and diversion in the RADARS System for the Drug Diversion, Key Informant, and Opioid Treatment Program Networks has been low and stable over time at less than 0.5 per 100,000 population. This rate is several times lower than that seen for hydrocodone and oxycodone, which in general have the highest rates of abuse. While there has been a

slight upward trend for tramadol in the Poison Control Center Data, it parallels the overall PCC data trend and again is much less than hydrocodone and oxycodone.

When ULTRACET® (tramadol/acetaminophen) is looked at specifically in the RADARS Poison Control Data, rates have been stable at 0.020 to 0.025 per 1000,000 population (Figure 6).

Figure 2: Drug Diversion Rates (per 100,000 population) Over Time – All RADARS System Opioids

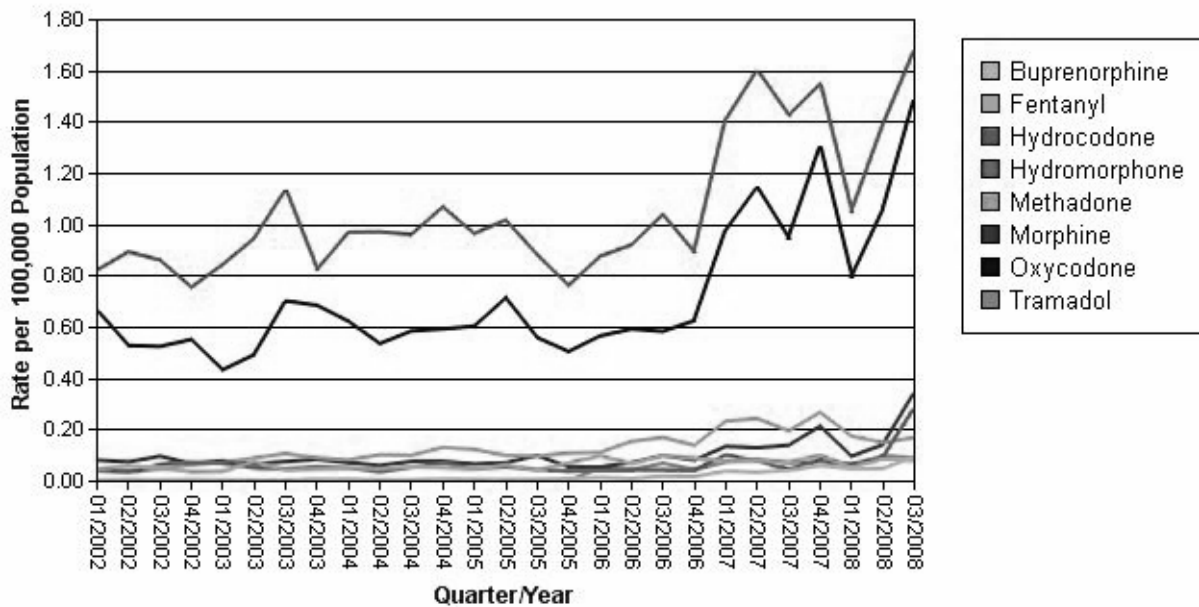


Figure 3: Key Informant Abuse Rates Over Time – All RADARS System Opioids

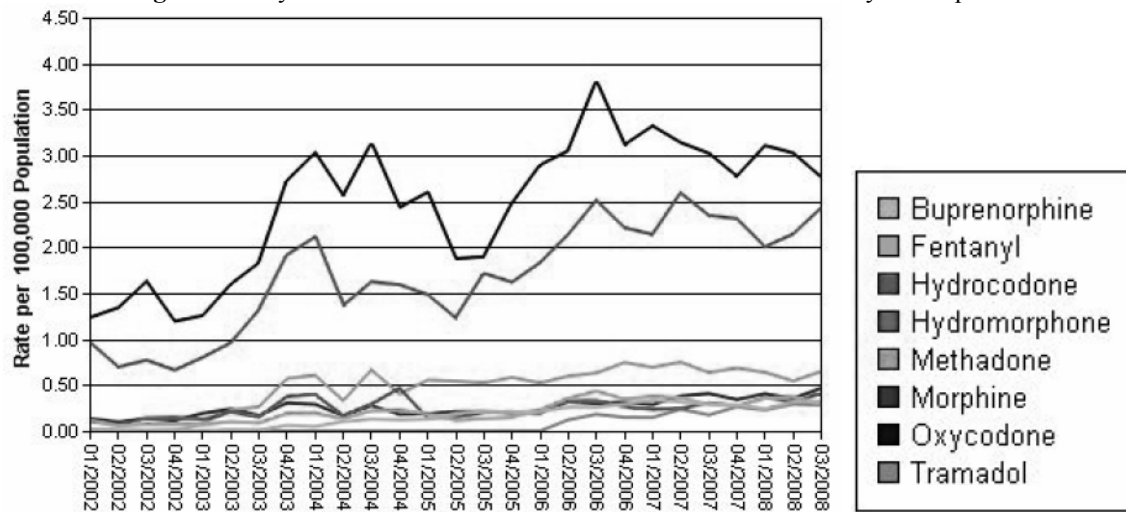


Figure 4: Poison Center Intentional Exposure Rates Over Time – All RADARS System Opioids

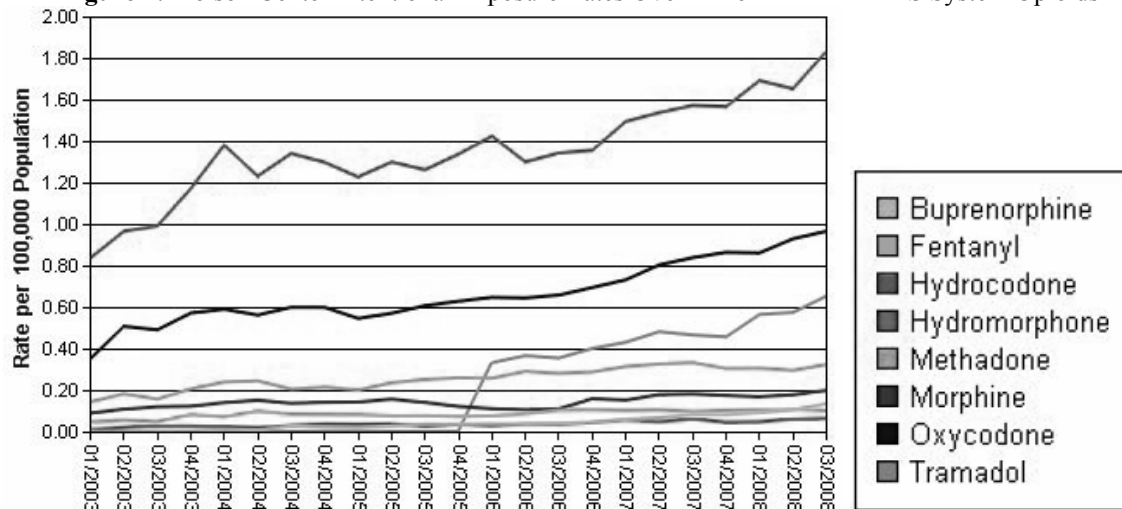


Figure 5: Opioid Treatment Program Abuse Rates Over Time – All RADARS System Opioids

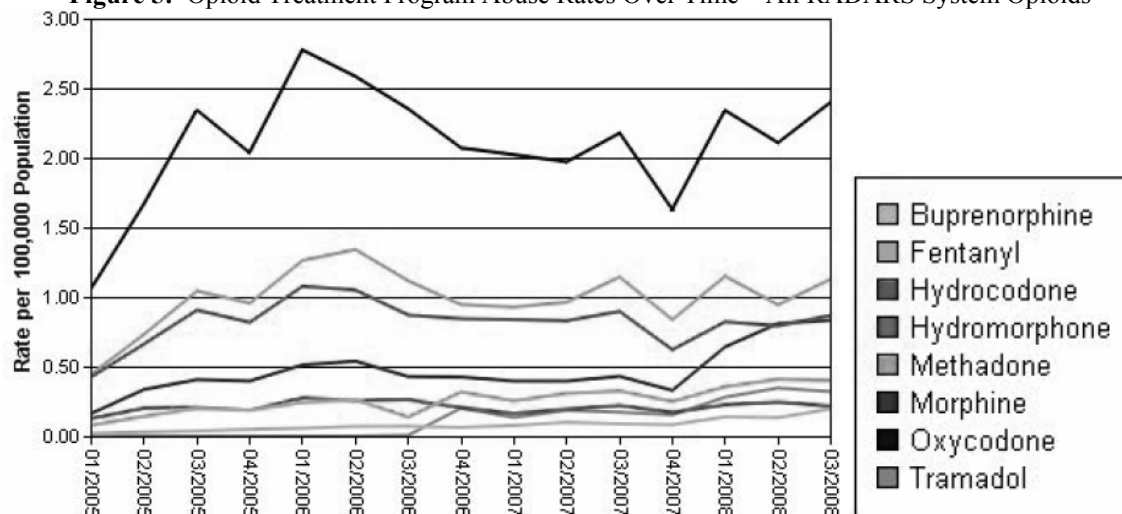
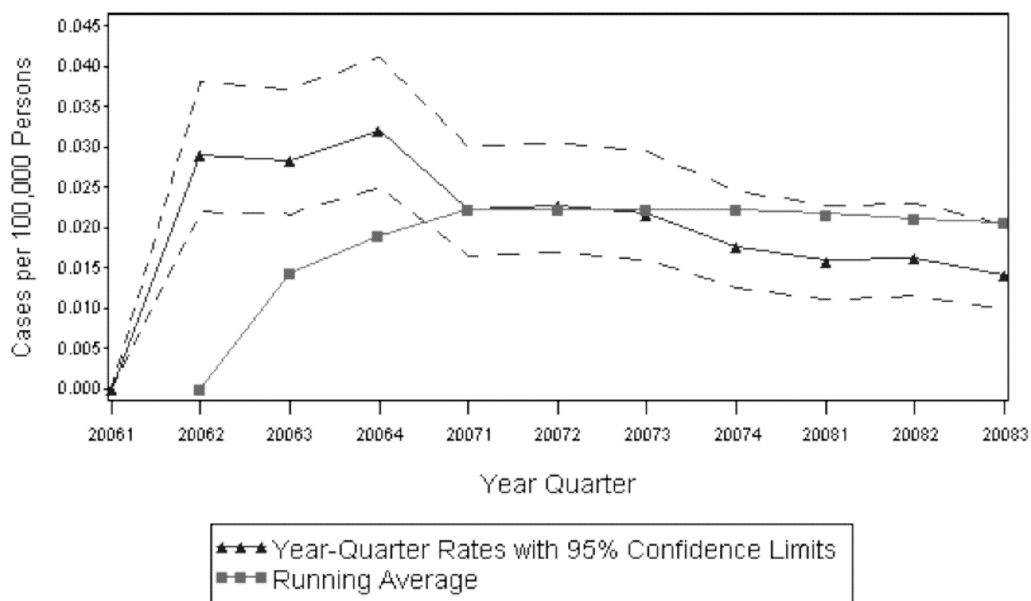


Figure 6: ULTRACET® Poison Center Trends Over Time

5.3.3.4 Ultracet Poison Center Trends Over Time (Rate per 100,000 Population) with 95% Confidence Intervals and Running Average



6. META-ANALYSES OF ACETAMINOPHEN COMBINATION PRODUCTS

Two meta-analyses have been performed on combination products containing acetaminophen at more than one dose.^{23,24}

6.1. Codeine and Acetaminophen Combination Product

Ortho-McNeil markets, TYLENOL® with Codeine, in two dosage strengths that contain 30 mg of codeine and 300 mg of acetaminophen (No. 3) and 60 mg of codeine and 300 mg of acetaminophen (No.4). Since this product was submitted as an ANDA, no additional efficacy data were submitted to support the superior analgesic effects of the combination compared to its individual components.

In the published literature, one meta-analysis included reports of randomized, double-blind, placebo-controlled clinical trials of codeine plus acetaminophen, compared with placebo or the same dose of acetaminophen alone in adults with acute postoperative pain.²³ Twenty-six studies that included 2295 subjects were included that compared codeine plus acetaminophen with placebo. Table 3 summarizes the results for the percent of subjects with at least 50% pain relief and the number needed to treat (NNT) for each dose of the codeine plus acetaminophen combination. The NNT for codeine 60 mg plus acetaminophen 800-1000 mg was 2.2 (95% CI, 1.8 – 2.9), for codeine 60 mg plus acetaminophen 600-650 mg was 3.9 (95% CI, 3.3 – 4.7), and for codeine 30 mg plus acetaminophen 300 mg was 6.9 (95% CI, 4.8 – 12). The combination containing codeine 60 mg plus acetaminophen 800-1000 mg was significantly superior to both codeine 60 mg plus acetaminophen 600-650 mg ($p<.0067$) and to codeine 30 mg plus acetaminophen 300 mg ($p<.0006$). This indicates that even in codeine-containing combination products, acetaminophen demonstrates a dose response effect with higher doses of acetaminophen providing greater pain relief.

Table 3: Meta-Analysis Results for Efficacy of Codeine Plus Acetaminophen Compared With Placebo²³

Dose of Codeine/Acetaminophen	At least 50% pain relief with		
	Codeine Plus Acetaminophen (%)	Placebo (%)	NNT (95%CI)
60 mg/800-1000 mg (N=192)	53	7	2.2 (1.8 - 2.9)
60 mg/600-650 mg (N=1413)	43	17	3.9 (3.3 - 4.7)
30 mg/300 mg (N=690)	32	18	6.9 (4.8 – 12)

CI = confidence interval, NNT = number of treat

Adverse events were mainly mild to moderate in severity and incidence did not differ between groups. No serious adverse events were reported. There was no significant difference between codeine plus acetaminophen and acetaminophen alone at any dose, or for all doses combined.

6.2. Oxycodone and Acetaminophen Combination Product

TYLOX®, a combination product marketed by Ortho-McNeil, contains 5 mg of oxycodone and 500 mg of acetaminophen. This product was submitted as an ANDA.

Therefore, no additional efficacy data were submitted to support the superior analgesic effects of the combination compared to its individual components.

One published meta-analysis included reports of randomized, double-blind, placebo-controlled, single dose clinical trials of oral oxycodone plus acetaminophen, compared with placebo or the same dose of oxycodone alone in adults with acute postoperative pain.²⁴ Four studies were included that compared oxycodone 5 mg in combination with acetaminophen 325 mg (76 subjects), 500 mg (78 subjects), and 1000 mg (40 subjects). Five studies were included that compared oxycodone 10 mg in combination with acetaminophen 650 mg (157 subjects) and 1000 mg (45 subjects). Table 4 summarizes the results for the percent of subjects with at least 50% pain relief and the NNT for each dose of the oxycodone plus acetaminophen combination. A dose-response relationship was not shown with increased doses of acetaminophen as indicated by overlapping confidence intervals of the NNTs. The authors state that this was probably due to the small number of trials and subjects in each trial.

Table 4: Meta-Analysis Results for Efficacy of Oxycodone Plus Acetaminophen Compared With Placebo²⁴

Dose of Oxycodone/Acetaminophen (Number of Trials)	Number of Subjects Treated with Combination	Number of Subjects Treated with Placebo	NNT (95%CI)
5 mg/1000 mg (N=1)	40	38	3.9 (2.1 - 20)
5 mg/500 mg (N=2)	78	72	2.2 (1.7 – 3.2)
5 mg/325 mg (N=1)	76	73	2.5 (2.0 – 3.4)
10 mg/1000 mg (N=1)	45	38	2.7 (1.7 – 5.6)
10 mg/650 mg (N=4)	157	160	2.5 (2.0 – 3.3)

Significantly more adverse events were reported with the combinations than with placebo for all doses except oxycodone 5 mg in combination with acetaminophen 325 mg. The numbers needed to harm were similar between oxycodone 5 mg and the two doses of acetaminophen (500 mg and 1000 mg) in combination and between oxycodone 10 mg and the two doses of acetaminophen (500 mg and 1000 mg) in combination. This indicated that the higher doses of acetaminophen did not result in increased numbers of adverse events.

7. POST-MARKETING SAFETY ANALYSIS OF HEPATOBILIARY RELATED ADVERSE EXPERIENCE

7.1. Introduction

The post-marketing data contained in SCEPTRE, part of the Benefit Risk Management (BRM) worldwide safety database, and involving hepatic injury occurring in patients receiving acetaminophen/codeine, oxycodone/acetaminophen, or tramadol/acetaminophen were reviewed.

7.2. Methods

A search of SCEPTRE was performed for all adverse event cases that met the following criteria:

- Cases reported in the United States and for which entry into SCEPTRE was completed as of 31 December 2008
- Tramadol/acetaminophen, acetaminophen/codeine, or oxycodone/acetaminophen as a suspect or suspect interacting medication
- Valid cases only
- Last distributed version
- Adverse events coded to a Medical Dictionary for Regulatory Activities (MedDRA version 11.1) Preferred Term (PT) within the Standardised MedDRA Query (SMQ) of Possible drug related hepatic disorders - comprehensive search

All cases were retrieved independent of the reporter's relationship attribution. In accordance with Company policy, all spontaneous cases are considered possibly related at the time of entry into the database and, therefore, individual assessments may not be in agreement with the causality assessment of the reporter. Because cases are classified as serious or nonserious at the case level, some may have the case designation of "serious" although the particular event of interest is not serious.

All cases identified by the search were reviewed and analyzed at the case level.

7.3. Results

A total of 40 cases were retrieved in the search of SCEPTRE. None of these cases involved pediatric patients.

Of the 40 cases, 1 case (20070901046) described an hepatic event that occurred prior to administration of the acetaminophen-containing product, 5 cases^a did not describe a hepatic injury, 7 cases^b contained insufficient information to make an assessment of the event, itself, or of the relationship between the event and the administration of the

a 20031203598, 20040701739, 20061207027, 20070604766, 20080106340

b 20040100757, 20040304807, 20040304812, 20040906644, 20050806391, 20051004354, 20070804166

acetaminophen-containing product (eg, no dates provided). These 13 cases are not further discussed.

Of the remaining 27 cases, 2 cases (20050901973, 20070104669) were eliminated from further review because the interpretation of the relationship between the hepatic event and acetaminophen was confounded by the use (abuse) of a concomitant medication (baclofen and opiates/benzodiazepines, respectively). Both of these cases reported increased liver function tests.

Of the remaining 25 cases, 10 cases^a reported an intentional acute ingestion of: acetaminophen/codeine + single ingredient acetaminophen (2 cases); tramadol/acetaminophen alone (2 cases); tramadol/acetaminophen + acetaminophen/hydrocodone (2 cases); oxycodone/acetaminophen alone (1 case); oxycodone/acetaminophen + acetaminophen (1 case); tramadol/acetaminophen + oxycodone/acetaminophen (1 case); and tramadol/acetaminophen + acetaminophen/propoxyphene (1 case). Four of the 10 cases reported multiple ingestions, specified to be 5 days (2 cases), a few days (1 case), and several days (1 case). All 4 cases reported fatal hepatic failure. Five of the 10 cases reported a single ingestion, including 1 case reporting increased liver function tests and a completed suicide. The other 4 cases reported transient increases in liver function tests. In the remaining case, which reported increased liver function tests, it was unclear if there was a single or multiple ingestions.

Of the 15 remaining cases, 5 cases^b reported an intentional acute ingestion, following a period of chronic use. All 5 cases reported single ingestion of: oxycodone/acetaminophen alone (2 cases); acetaminophen/codeine alone (1 case); acetaminophen/codeine + acetaminophen + acetaminophen/hydrocodone (1 case); and oxycodone/acetaminophen + acetaminophen/hydrocodone (1 case). All 5 cases reported fatal hepatic failure.

Of the remaining 10 cases, 1 case (20040903702) reported an unintentional acute ingestion, following a period of chronic use. Based on description of this 79 year-old patient's history of liver failure, it appears that this is a patient with compensated liver failure, who had been taking acetaminophen for a long time. An unintentional overdose (medication error) occurred, involving multiple ingestions of oxycodone/acetaminophen and acetaminophen over a 36-hour period. The reported hepatic event was increased bilirubin. The patient died 11 hours after initial presentation.

^a 20040903450, 20040908882, 20040908885, 20050902538, 20050902676, 20061005700, 20070104700, 20070104851, 20081004911, 20081004942

^b 20060901823, 20060901838, 20060901895, 20060901824, 20060901843

Of the remaining 9 cases, 3 cases^a reported an unintentional acute ingestion. All 3 cases reported fatal hepatic failure. They described administration of: acetaminophen/codeine alone at a dose of 7.5 g/day for 24-48 hours; acetaminophen/codeine + acetaminophen in a patient reported to be “overusing acetaminophen/codeine for pain” and with an acetaminophen level of 392 mcg/mL; and tramadol/acetaminophen + acetaminophen/codeine + acetaminophen in a single ingestion.

Of the remaining 6 cases, 4 cases^b reported chronic use, only. One case reported use of acetaminophen/codeine for 4.5 years, and reported “liver disorder”. Two cases reported use of tramadol/acetaminophen for 1 year and oxycodone/acetaminophen for 2 years, respectively; both reported increased liver function tests. The remaining case reported use of acetaminophen/codeine for 10 years (single-ingredient acetaminophen was also reported as a cosuspect medication). The reported event was hepatic cirrhosis, but the case narrative stated that the cirrhosis was “diagnosed by bloodwork”.

Of the remaining 2 cases, 1 case (20070805369) reported acute use of a therapeutic dose (exact dose not specified) in a patient treated post-operatively with oxycodone/acetaminophen for a period of 9 days. The patient experienced a transient increase in liver function tests.

The final case (20050901920) reported use of oxycodone/acetaminophen and hepatic failure secondary to acetaminophen, but did not report whether administration was acute or chronic, or include other details to further assess the case.

7.4. Conclusions of Postmarketing Safety Analysis

Of the 25 cases describing hepatic injury and with sufficient information to perform an assessment, 15 (60%) cases reported acute intentional overdose. Two-thirds of these cases did not provide a history of chronic acetaminophen use while the other third did. Six (40%) of the 15 cases reported use of tramadol/acetaminophen, of which 4 (67%) cases reported concomitant use of other acetaminophen products. Six (40%) of the 15 cases reported use of oxycodone/acetaminophen, of which 3 (50%) reported concomitant use of other acetaminophen products.^c Four (27%) of the 15 cases reported use of acetaminophen/codeine, of which 3 (75%) reported concomitant use of other acetaminophen products.

^a 20050901977, 20060901922, 20060901942

^b 20060500383, 20060806408, 20070307148, 20080404473

^c Note that one of the 15 cases reported concomitant use of tramadol/acetaminophen and oxycodone/acetaminophen and is therefore represented in both of these groups.

Four (16%) of the 25 cases reported acute unintentional overdose. One of these cases reported use of a single product (acetaminophen/codeine), while the remaining 3 cases reported concomitant use of multiple prescription and over-the-counter acetaminophen-containing products (oxycodone/acetaminophen + acetaminophen; acetaminophen/codeine + acetaminophen; tramadol/acetaminophen + acetaminophen/codeine + acetaminophen).

The remaining 6 (24%) of the 25 cases described patients chronically taking acetaminophen-containing opioid products and subsequently developing various liver abnormalities (eg, elevated liver function tests, cirrhosis).

8. CONCLUSIONS

Various pain guidelines include the use of combination analgesics because they provide multimodal pain control that may be superior to that provided by single entity analgesics. In addition, by using a combination of analgesics one can achieve a shorter onset and longer duration of pain control than that provided by the individual components alone, thereby providing the same degree of analgesia with reduced doses of the individual components. This reduction in dose may be associated with a reduction in the incidence of adverse events. Studies have shown that the combination of tramadol and acetaminophen provides all of these advantages. Combination analgesic therapy also allows for the transitioning of opioid-naïve patients from nonsteroidals and acetaminophen (step one analgesics in the WHO pain ladder) to single-entity Schedule II opioids (step three analgesics in the WHO pain ladder).

Provision of combination analgesic therapy as a fixed-dose combination product is preferable compared to use of single-entity products since compliance is enhanced, medication errors may be reduced, and use of the most appropriate ratio of one analgesic to another is ensured. If fixed-dose combination products were not available, the optimal use of combination therapy would be impaired.

ULTRACET® is a non-scheduled analgesic approved for moderate to severe acute pain in the US. Compared to other opioids (full or partial mu-agonists), the abuse liability of tramadol is low and has remained low for more than 30 years of marketing worldwide. ULTRACET® contains lower doses of both tramadol (37.5 mg) and acetaminophen (325 mg) than the standard strengths of the individual components (50 mg and 500 mg, respectively). When taken as recommended in the current ULTRACET® product labeling, the maximum daily dosage of acetaminophen would be 2600 mg, much lower than the currently approved dosage of 4000 mg/day for OTC use, and lower than the

maximum daily dosage of acetaminophen recommended by the Acetaminophen Hepatotoxicity Working Group.

TYLENOL® with Codeine contains 30 or 60 mg of codeine and 300 mg of acetaminophen per tablet. The current recommended regimen and maximum dosage, as stated in the US prescribing information for TYLENOL® with Codeine, would be adjusted to meet the daily dosage maximum recommended by the Working group. In addition, the recommendations by the FDA/CDER working group for prescription combination products, such as unit of use packaging, can be implemented.

Each TYLOX capsule contains 5 mg of oxycodone HCl and 500 mg of acetaminophen. The current US Prescribing Information recommends the following: “The usual adult dosage is one TYLOX capsule every 6 hours as needed for pain ...”, with no stated maximum. This recommendation could be modified to, “The usual adult dosage is one TYLOX capsule every 6 hours as needed for pain. The daily dosage should not exceed a maximum of 6 capsules per day.” This provides a maximum of 3000 mg of acetaminophen per day, still less than the 3250 mg recommended by the Working Group. TYLOX, being a schedule 2 controlled drug, is prescribed in a controlled setting, wherein prescribers can emphasize such a maximum recommended daily dosage. In addition, the recommendations by the FDA/ CDER working group for prescription combination products containing 500 mg of acetaminophen, such as unit-of-use packaging, can be implemented.

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APPENDIX 1

NARRATIVES FOR TRAMADOL/PARACETAMOL-EXPOSED SUBJECTS WITH TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST RELATED TO THE HEPATOBILIARY SYSTEM IN ALL SINGLE-DOSE AND MULTIPLE-DOSE TRIALS

Subject 26004 (Lee, Protocol TRAMAP-ANAG-006, abnormal hepatic function):

This was a 64-year-old White female, weighing 77 kilograms, with a history of hypertension, hypercholesterolemia, a urinary tract infection, poison ivy, arthritis pain in her arms, hands and knees as well as low back pain since 1995. The subject was randomised to Tramadol/Paracetamol and withdrew voluntarily on Day 28 after seven days on therapy (reason = other: exclusionary drug taken along with study drug). The subject took one tablet of Tramadol/Paracetamol on Day 1, three tablets on Day 2, and one tablet on Day 5 prior to her withdrawal from the study. Concomitant medications taken before and during the study included Procardia one tablet daily and Mevacor 20 mg daily. The subject took prednisone tapering from three 5-mg tablets daily for two days to two tablets for four days and applied Elocon topically, prestudy for poison ivy. The subject then took both medications again on Day 5 for poison ivy that started that day and resolved on Day 14. The subject also took sulfamethoxazole one tablet twice daily prestudy for urinary tract infection (UTI) and again on Day 5 for a UTI that started that day and resolved on Day 15. At the scheduled chemistry interval on Day 28, the subject was had an elevated postbaseline ALAT of 98 U/L (normal range of 0 to 48 U/L), an ASAT of 68 U/L (normal range of 0 to 48 U/L), and an alkaline phosphatase of 128 U/L (normal range of 15 to 110 U/L). The ALAT was identified as a markedly abnormal laboratory test value according to predetermined criteria and was reported as an adverse event of marked severity, although the subject had no symptoms. Baseline testing performed six days prior to taking study drug had been normal with an ALAT of 18 U/L, an ASAT of 16 U/L, and an alkaline phosphatase of 92 U/L. This subject returned on Day 62 (five weeks after completing the study) for unscheduled follow-up chemistry lab testing. At that time the liver function tests were normal with an ALAT of 19 U/L, an ASAT of 16 U/L, and an alkaline phosphatase of 94 U/L. The investigator considered this treatment-emergent adverse event to be possibly related to the study drug.

Subject 44003 (Hoffstetter/Stark, Protocol TRAMAP-ANAG-006): This was a 72-year-old White male, weighing 94 kilograms, with a history of colon cancer in 1965, chronic pain of osteoarthritis in the hands and knees, lumbo-sacral spine fusion, and low back pain since 1980. Concomitant medication included ibuprofen two 200-mg tablets prn for joint stiffness. The subject was noted to have an elevated postbaseline LDH of 594 U/L (normal range of 0 to 270 U/L) in a hemolysed chemistry lab specimen drawn as scheduled upon his completion of the four-week double-blind study on Day 29. The LDH was identified as a markedly abnormal laboratory test value according to predetermined criteria. The baseline testing performed seven days prior to taking study drug had been normal. This subject returned on Day 50 (three weeks after completing the double-blind portion of the study) for an unscheduled follow-up chemistry lab testing. At that time the liver function tests were normal with an LDH of 155 U/L, despite the subject's continuing to take the Tramadol/Paracetamol combination study drug in an open-label extension study. The increased LDH was not reported as an adverse event.

Subject 47001 (Zuzga, Protocol TRAMAP-ANAG-006): This was a 58-year-old White female, weighing 105 kilograms, with arthritis of the left shoulder, hands, feet and low

back and a history of glaucoma, sinus congestion, bronchitis, hypertension, constipation, hemorrhoids, and depression. Concomitant medications included multiple vitamins and supplements, Fibroplex three tablets daily, Metamucil two teaspoons daily, Caltrate plus two tablets daily, DynaCirc 5 mg daily, Co-enzyme Q 120 mg daily, and aloe one 400 mg capsule daily. The subject was noted to have an elevated postbaseline ALAT of 80 U/L (normal range of 0 to 48 U/L), an ASAT of 49 U/L (normal range of 0 to 41 U/L), and an alkaline phosphatase of 119 U/L (normal range of 15 to 110 U/L) in the scheduled chemistry lab drawn upon her completion of the four-week double-blind study on Day 29. The ALAT was identified as a markedly abnormal laboratory test value according to predetermined criteria. Baseline testing performed six days prior to taking study drug had been normal with an ALAT of 30 U/L, an ASAT of 24 U/L, and an alkaline phosphatase of 86 U/L. This subject returned on Day 46 (three weeks after completing the study) for an unscheduled follow-up chemistry lab testing. At that time the liver function tests were normal with an ALAT of 37 U/L, an ASAT of 22 U/L, and an alkaline phosphatase of 89 U/L despite the subject's continuing to take the Tramadol/Paracetamol combination study drug in an open-label extension study. The elevated ALAT was not reported as an adverse event.

Subject 54002 (Lane, Protocol TRAMAP-ANAG-006, abnormal hepatic function):

This was a 37-year-old White male, weighing 64 kilograms, with chronic pain of osteoarthritis of the left ankle. The subject also had a history of intermittent colitis (irritable bowel syndrome) and surgical repair of left ankle in 1981 following an automobile accident. The subject was randomised to Tramadol/Paracetamol and completed the study after 758 days on therapy. Concomitant medications included Valium 10 mg twice daily starting on Day 149 for hypertonia (back spasm of marked severity on Days 149 through Day 179); ibuprofen 800 mg starting Day 233 for marked pain starting that day following a dental visit and resolving Day 246; Oxycodone starting on Day 751 for pain of dental crown replacement that day through Day 753; Alovora cream starting Day 755 for moderate acid burns on hands that day that resolved Day 782; and Bactrim (starting September 1997), Floxin (October through November 1997), and Septra DS (starting December 1997) for chronic prostatitis of marked severity that started September 1997 (September 97 = Days 428 through 457) and persisted. The subject also reported mild seborrhoea Days 3 through 32; mild scratchy throat Days 13 through 63, withdrawal syndrome of moderate severity on Days 16 through 17; moderate leg fatigue Days 44 through 81; mild insomnia starting Day 46 that resolved after approximately eight months; mild withdrawal symptoms when off drug for 24 hours starting Day 164 and resolving Day 492; moderate influenza-like symptoms Days 434 through 439; infected tooth Days 498 through 503 and 544 through 549; and acid burns of moderate severity on hands on Day 755 that resolved on Day 782. The subject also had abnormal liver function tests not otherwise specified (elevated ALAT [SGPT] and ASAT [SGOT]) and occult blood in urine on Day 29. Both the elevated ALAT and occult blood resolved by Day 88 and the increased ASAT persisted. The subject's ALAT value was normal (17 U/L, normal range = 0 to 48 U/L) at Screening on Day -5, increased to 57 U/L on Day 29, returned to normal (17 U/L) by Day 88, and remained normal throughout the remainder of the study. The subject's ASAT results were normal (14 U/L, normal range =

0 to 41 U/L) at Screening and remained within the normal range (values ranged from 14 to 25 U/L) throughout the study. The subject's urine occult blood result was negative at Screening, trace on Day 29, and negative on Day 58. No red blood cells (RBCs) were seen in the urine on these days. On Day 654, the urine occult blood was trace and 1 to 3 RBCs per high power field were seen in the urine. The urine occult blood was negative and no RBCs were seen in the urine on Day 758. According to the investigator the insomnia and withdrawal symptoms were certainly related to study medication; the seborrhoea, elevated ALAT, and elevated ASAT were probably/likely related; the scratchy throat and urine occult blood were possibly related; and the prostatitis, muscle weakness, back spasm, influenza-like symptoms, dental pain, infected tooth, tooth erosion, and acid burns were unlikely related. The subject's alkaline phosphatase and bilirubin were in the normal range throughout the study.

Subject 54003 (Lane, Protocol TRAMAP-ANAG-006, bilirubinaemia): This was a 60-year-old White male, weighing 54 kilograms, with chronic lower back pain. He also had a history of occasional sinusitis due to chronic respiratory allergies. The subject was randomised to Tramadol/Paracetamol and completed the study after 718 days on therapy. Concomitant medications included Nyquil and Tavist both starting on Day 134 for an upper respiratory tract infection of moderate severity and unlikely relationship to study medication that onset on Day 134 and resolved Day 148. The subject had mild nausea and constipation on Days 319 through 320. It was noted that the subject took two study drug pills at once. The investigator considered these adverse events were probably/likely related to study medication. The subject had mild nausea and constipation again on Days 379 through 386 that were possibly related to study medication. The subject also had several intervals of bilirubinaemia, intermittent increased serum cholesterol, increased NPN (nonprotein nitrogen [serum creatinine]), and a single instance (Day 31) of albuminuria. All were mild in severity and possibly related to study medication. The subject's bilirubin level was above normal at Screening on Day -5 (1.5 mg/dL, normal range = 0.8 to 1.3 mg/dL), increased to 2.0 mg/dL on Day 31, then returned to normal (1.2 mg/dL) on Day 60. The bilirubin was above normal (1.7 mg/dL) on Day 88, normal (1.3 mg/dL) by Day 164, above normal (1.9 mg/dL) on Day 249, and remained above normal for the remainder of the study (range = 1.4 to 1.9 mg/dL). At the last visit on Day 718, the bilirubin was 1.9 mg/dL. The subject's cholesterol was slightly high at Screening on Day -5 (200 mg/dL, normal range = 0 to 199 mg/dL) and was above the normal range at all test intervals (range = 202 to 241 mg/dL) except the Final Visit on Day 718 when it was 192 mg/dL. The subject's creatinine value was normal on Day -5 (1.3 mg/dL, normal range = 0. to 1.5 mg/dL) and at all study intervals (range = 1.3 to 1.5 mg/dL), but was at the upper limit of normal (1.5 mg/dL) on Days 31 and 60. The subject's urine protein was +1 on Day 31, returning to normal (negative) by Day 60. The subject's alkaline phosphatase, ASAT, and ALAT were in the normal range throughout the study.

Subject 18001 (Resnick, Protocol TRAMAP-ANAG-015, abnormal hepatic function): This was a 41-year-old Hispanic female, weighing 79 kilograms, with a history of osteoarthritis of both hands (1996) and low back pain (1995). The only concomitant medication was Depo Provera, 150 mg/mL for birth control. The subject was

randomised to Tramadol/Paracetamol and completed the study after 183 days on therapy. The subject had normal ALAT (30 U/L, normal range 0 to 48 U/L) and ASAT (28 U/L, normal range 0 to 42 U/L) levels at Screening on Day -5. The subject's ALAT and ASAT levels were normal (both 19 U/L) on Day 93, but increased to 60 U/L and 49 U/L, respectively on Day 183. Both liver enzymes returned to the normal range (38 U/L and 32 U/L, respectively) at an unscheduled follow-up test on Day 191. All other laboratory values, including alkaline phosphatase and bilirubin remained in the normal range throughout the study. The investigator considered the treatment-emergent adverse events, hepatic function abnormal, liver function tests abnormal not otherwise specified, to be of mild severity and possible relationship to study to the study drug.